The Infectious Dose of *Coxiella burnetii* (Q Fever)

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Abstract

Quantitative estimation of an individual's risk of infection due to airborne pathogens requires knowledge of the pathogen's infectious dose, in addition to estimates of the pathogen's airborne concentration and the person's exposure duration. Based on our review of the published literature on Q fever, we conclude that the infectious dose of Coxiella burnetii *is likely one rickettsia, and that the probability of a single organism initiating infection is approximately 0.9. Findings in experiments exposing guinea pigs to* C. burnetii *via intraperitoneal injection and inhalation of respirable aerosols firmly support a "one-hit" Poisson model of infection. Findings in experiments exposing human subjects to* C. burnetii *via inhalation of respirable aerosols fail to provide convincing evidence that the one-hit Poisson model applies to human infection; however, inference from the human studies is limited by the small numbers of subjects and lack of quantification of the exposure concentrations. Given the presence of* C. burnetii *in sputum, the prevalence of cough in Q fever patients, and the ability of the pathogen to initiate infection via the respiratory tract, we believe that person-to-person transmission of* C. burnetii *via inhalation of respiratory aerosol is possible.*

Introduction

Coxiella burnetii, the causative agent of Q fever, was developed for use as a biological weapon in the United States, Japan, and the former Soviet Union. Although Q fever is rarely lethal, *C. burnetii* has a low infectious dose, is easily dispersed through the air, and can cause substantial morbidity in an exposed population (Kagawa, Whehner, & Mohindra, 2003). The World Health Organization (1970) has estimated that aerosol dispersal of 50 kg of *C. burnetii* over a metropolitan area with approximately 5 million inhabitants would result in 250,000 incapacitating casualties and 250 deaths. Human infection by the respiratory route has been demonstrated with respirable particles with diameters less than 10 μm (Tigertt & Benenson, 1956; Tigertt, Benenson, & Gochenour, 1961), and epidemiological studies have documented airborne transmission of Q fever to persons by infected livestock (Dupis et al., 1987; Meiklejohn et al., 1981; Salmon, Howells, & Glencross, 1982; Selvaggi et al., 1996; Tissot-Dupont et al., 1999). Q fever is common among workers in livestock and animal products trades pertaining to cows, sheep, and goats (Derrick, 1937; Gilroy et al., 2001; Janton, Bondi Jr., & Sigel, 1949; Sigel et al., 1950; Topping, Shepard, & Irons, 1947), and among deployed armies (Bayer, 1982; Splino, Beran, & Chlibek, 2003). Q fever also occurs among laboratory workers in medical and microbiological research facilities (Bayer, 1982; Hall, Richmond, & Caul, 1982; Huebner, 1947; Johnson & Kadull, 1966; Oliphant et al., 1949; Robbins & Rustigian, 1945; Simor et al., 1984).

The Centers for Disease Control and Prevention (2004) states that person-to-person transmission of *Coxiella burnetii* is "rare." We identified published reports of person-to-person Q fever transmission in the circumstances of postmortem examinations (Gerth, Leidig, & Riemenschneider, 1982; Harman, 1949), transplacental infection (Raoult & Stein, 1994), and sexual contact (Kruszewska, Lembowicz, & Tylewska-Wierzbanowska, 1996; Milazzo et al., 2001). In addition, Deutsch and Peterson (1950) reported Q fever occurring in three persons 14 to 23 days subsequent to attending an acutely ill Q fever patient, and Osorio et al. (2003) described a case of nosocomial transmission of Q fever between two patients. Familial clusters identified in epidemiological studies have typically been explained as involving a common environmental exposure. Mann et al. (1986) described the following sequence of Q fever incidence among family members, which suggests person-to-person transmission. A man employed as a shepherd had an aysmptomatic case of Q fever. Next, his wife and daughter developed Q fever, which possibly involved exposure to *C. burnetii* brought home on his work clothes. However, the man always changed his clothes before visiting his parents-in-law who became ill 7 and 12 weeks, respectively, subsequent to the illness of his immediate family members.

In determining airborne infection control procedures, it is useful to quantitatively estimate infection risk, if possible, where risk depends on the pathogen's infectious dose, the pathogen's airborne concentration, and the duration of exposure. In this paper the authors argue that the infectious dose of *C. burnetii* is on the order of one organism. Therefore, given an estimate of airborne exposure intensity and the duration of exposure to *C.*

burnetii due to laboratory procedures, one can evaluate existing biosafety protocols. We also argue that person-to-person transmission of Q fever is possible given the low infectious dose and the presence of *C. burnetii* in the bodily fluids of some infected patients. Although the risk of secondary airborne infection from respiratory fluids may be low, in general, due to low pathogen concentrations in respiratory fluid, the risk of secondary airborne infection during delivery may be more significant due to the relatively high potential for placental infection.

Background on Q Fever

Q fever was originally described in 1935 by E. H. Derrick who investigated a number of cases of fever among workers in a large abattoir in Brisbane, Australia (Derrick, 1937). The illness was characterized by acute onset, with high fever and intense headache. The causal organism was identified as a rickettsia by Burnet and Freeman in 1937. They observed the organism to be rods less than 1 μm in length and 0.3 μm in diameter, but noted that the shape varied from rods to coccoid forms. Like viruses, small numbers of the organisms were able to pass through filtering membranes. In 1939, Derrick proposed the name *Rickettsia burneti* (Zdrodovskii & Golinevich, 1960). *Rickettsia diaporica*, the filter-passing infectious agent isolated from Rocky Mountain wood ticks collected near Nine Mile Creek, Montana that caused "American" Q fever, was eventually determined to be the same organism as *R. burneti*, and in the late 1940s the organism was renamed *Coxiella burnetii* when the classification of rickettsiae was revised (Philip, 1948).

Infection by *C. burnetii* can be accomplished through tick bite, inhalation of aerosolized organisms, ingestion of contaminated materials, and sexual contact. Q fever is the only tick-borne rickettsial disease that develops without a primary infectious focus in the bite area (Khavkin, 1990). The primary route of human exposure is through the air, and like the other routes of exposure can lead to acute or chronic Q fever. Acute Q fever is a systemic disease, which is typically self-limited and characterized by fever, severe headache, fatigue, and chills (Marrie, 1990). Some fraction of cases, with estimates ranging from 4% to 83% (Fiset & Woodward, 1998), develop pneumonia; of the latter cases, 30% to 40% have a productive cough (Marrie, 2003). The classical case description includes a dry cough but mixed infection can occur with *Staphlococcus pneumoniae* and other organisms implicated in community-acquired pneumonia (Okimoto et al., 2004), which may explain the frequency of productive cough. *C. burnetii* has been recovered from sputum (Fiset & Woodward, 1998; Steinmann, 1951). The treatment of choice is doxycycline (Centers for Disease Control and Prevention, 2004), yet without treatment, mortality due to acute Q fever is less than 1% (Fiset & Woodward, 1998; World

Health Organization, 1970). Chronic Q fever presents as hepatitis (Dupont et al., 1971) or endocarditis. The latter condition is associated only with certain strains of the organism (Fiset & Woodward, 1998). In addition, a post-Q fever debility syndrome is seen following 20% to 40% of acute Q fever cases (Ormsbee & Marmion, 1990).

Because *C. burnetii* is an atypical rickettsiae, it is the only agent in the genus *Coxiella*. The organism is pleomorphic, enabling it to pass through filters with an average pore diameter as small as 400 nm (McCaul, 1991). The small cell variant of the organism is metabolically inactive outside of host cells and remains viable in the environment for long periods of time. It exhibits antigenic phase variation, similar to the smooth-rough variation in bacteria. In nature, *C. burnetii* is found primarily in phase I, the phase with the smooth structural form of lipopolysaccharide (LPS) in its cell wall; the organism is found in phase II, the rough LPS form, after infection of a host and is selected for in cell cultures (Fiset & Woodward, 1998; Williams, 1991). Phase II organisms have the ability to multiply in the phagolysosome of eukaryotic cells, but they cannot revert to phase I, which limits their infectivity in immunocompetent hosts (Ormsbee & Marmion, 1990). *C. burnetii* infection leads to the production of antibodies against both phases, with the appearance of phase II antibodies preceding the appearance of phase I antibodies in acute Q fever, and the reverse for chronic Q fever (Centers for Disease Control and Prevention, 2004).

Experimental Airborne Infection

The airborne infection and pathogenesis of *C. burnetii* in cynomolgus monkeys (*Macaca fascicularis*) was investigated by Gonder et al. (1979) in an effort to identify a primary model for evaluating prototype Q fever vaccines. Monkeys were exposed to small particle aerosols through a head mask for 1 minute. The inhaled dose was estimated to be the product of the monkey's respiratory volume (L min^{-1}), exposure duration (1 min), and the rickettsiae concentration (number L^{-1}) in the aerosol sample; the latter concentration was measured by an impinger sampling in the exposure apparatus and subsequent intraperitoneal assay in mice. All 10 monkeys exposed to 10^5 mouse median infectious doses developed overt clinical illness, while only one of four monkeys exposed to 10^3 mouse median infectious doses developed an elevated temperature, anorexia, and depression. While this study did not identify *M. fascicularis* to be highly sensitive to *C. burnetii*, it did confirm the potential for *C. burnetii* to infect primates through the respiratory tract.

Airborne infection of humans by *C. burnetii* has been demonstrated by Tigertt and Benenson (1956), who exposed groups of young men to 10 L samples of aerosol of the AD strain of the organism generated from whole-egg slurry. The particle size of the aerosol was not reported in

this study, but another paper by some of the same authors (1961) reported that the aerosols were composed primarily of particles on the order of 1 µm in diameter. Tigertt and Benenson (1956) observed that the inhaled dose that produced infection in 50% of exposed guinea pigs, produced infection in four of five exposed men, two of whom developed clinical disease. This finding suggests that the human median infectious dose is of the same order of magnitude as the median infectious dose in guinea pigs. The incubation period of Q fever was found to be inversely related to the dose.

The Infectious Dose

A microbe's infectious dose is frequently discussed in terms of the median infectious dose, or that dose producing infection in 50% of exposed susceptible hosts (the ID_{50}). However, the infectious unit, which is the smallest number of organisms capable of producing infection in a susceptible host, should also be considered. For *C. burnetii*, there is evidence that both of these dose metrics are on the order of one organism. In particular, Ormsbee et al. (1978) found that the median infectious dose in mice and guinea pigs exposed to phase I *C. burnetii* via intraperitoneal injection was 0.5 to 2 organisms. Scott, Williams, and Stephenson (1987) investigated the virulence of phase I Nine Mile strain *C. burnetii* in several strains of mice following intraperitoneal inoculation, and found increased antibody titers to whole-cell phase I and phase II *C. burnetii* 30 days after injection with a mean dose of 0.5 organisms.

In view of these observations, we hypothesize that infection by *C. burnetii* follows a one-hit model of infection, similar to that of variola (smallpox) virus (Nicas et al., 2004). A one-hit model of infection implies that a single organism is capable of initiating infection in a sus-

ceptible host. We assume that the dose received is a Poisson random variable, which is a reasonable assumption for an animal exposed via inhalation to infectious agents, and that each organism received has a probability κ of initiating infection. The probability of infection, p, is modeled as follows:

(1) $\quad$ $p = 1 - \exp(-\lambda \, \kappa)$

where λ is the average (expected) number of pathogens received by the host.

To evaluate this model, we examined data reported by Tigertt, Benenson, and Gochenour (1961) from studies in which groups of guinea pigs were exposed to *C. burnetii* via intraperitoneal injection versus inhalation. For the intraperitoneal injection route, 11 groups each containing 20 guinea pigs were exposed to two-fold serial dilutions of slurry from an egg culture of *C. burnetii*, and infection was assayed by serological response 30 days post-exposure (Table 1). Infection in each dose group was modeled as Binomial (20, p_i), where p_i is the probability of infection in the ith dose group. The maximum likelihood estimate of p_i is simply the proportion of infected animals:

$$\hat{p}_i = x_i / n_i$$

where x_i is the observed number of infections among n_i number of animals exposed (in this case, $n_i = 20$). The one-hit model is:

(2) $\quad$ $p_i = 1 - \exp(-c_0 \, d_i \, v \, \kappa)$

where c_0 is the concentration of organisms in the undiluted inoculum, d_i is the dilution factor for i^{th} dose group, and v is the volume of inoculum administered. The prod-

Table 1

Experimental Data and Expected Responses of Guinea Pigs Exposed to *C. burnetii* via Intraperitoneal Injection

Dose Group	Dilution (d_i)	a_i	Observed Response[*]	$\hat{p}_i$	$p_i(\hat{M})$	Expected Response[*]
1	$10^{-9.3}$	1	20	1	0.99	20
2	$10^{-9.6}$	½	19	0.95	0.99	20
3	$10^{-9.9}$	¼	17	0.85	0.90	18
4	$10^{-10.2}$	1/8	16	0.80	0.69	14
5	$10^{-10.5}$	1/16	8	0.40	0.44	8.5
6	$10^{-10.8}$	1/32	7	0.35	0.25	5.1
7	$10^{-11.1}$	1/64	4	0.20	0.14	2.7
8	$10^{-11.4}$	1/128	1	0.05	0.07	1.4
9	$10^{-11.7}$	1/256	1	0.05	0.04	0.72
10	$10^{-12.0}$	1/512	1	0.05	0.02	0.36
11	$10^{-12.3}$	1/1024	0	0	0.01	0.18

*Infected out of 20 exposed

uct $c_0 \times d_i \times v$ is the predicted dose (number of organisms received) in the ith exposure group. Because the quantity $c_0 \times v \times \kappa$ is a constant across the dose groups, it is set equal to M. Additionally, we can replace the term d_i by α_i, where α_i is the relative dilution of the inoculum, and $\alpha_i \times d_1 = d_i$. Thus, the one-hit model is written more simply as:

$$(3) \qquad p_i = 1 - \exp(-\alpha_i M)$$

An estimate of M, denoted $\hat{M}$, can be obtained which maximizes the log-likelihood of the joint distribution function. The likelihood (joint distribution) function is:

$$Lik(M) = \prod_{i=1}^{11} \binom{n_i}{x_i} p_i^{x_i}(1-p_i)^{n_i-x_i} =$$

$$\prod_{i=1}^{11} \binom{n_i}{x_i}(1-e^{-M\alpha_i})^{x_i}(e^{-M\alpha_i})^{n_i-x_i}$$

In turn, taking the natural logarithm of both sides of the above equation leads to:

$$\ln(M) \propto \sum_{i=1}^{11} x_i \ln\left(1-e^{-M\alpha_i}\right) - (n_i - x_i)M\alpha_i$$

The estimate $\hat{M}$ was determined to be 9.346, and the probability of infection expected under the one-hit model was calculated by substituting this value for M into Equation 3. Table 1 presents the expected probabilities of infection $p_i(\hat{M})$ under the model, and the expected number of infections given 20 exposed guinea pigs per dose group. The predicted infection response compares well with the observed response (Figure 1). This similarity was confirmed by a Pearson's chi-square statistic, $\chi^2_6 = 1.757$, where the subscript 6 denotes six degrees of freedom, or one less than the seven dose groups analyzed to account for the estimation of one parameter. Note that the original dose groups 7 through 11 in Table 1 were combined to achieve a minimum of 5 expected responses per dose group, which is a standard procedure for computing a chi-square statistic. The statistic $\chi^2_6 = 1.757$ has an associated *p*-value of 0.941, which signifies that the observed response data do not differ significantly from the response data predicted by the one-hit model with M = 9.346.

For comparison, we also fit two multi-hit models of infection which assume that, respectively, two or three organisms are required to initiate infection in a susceptible host. As with the one-hit model, we assume that the dose received is a Poisson random variable such that the probability of infection p is modeled as follows:

Figure 1

Observed infection frequencies in guinea pigs exposed via intraperitoneal injection and infection frequencies expected from the one-hit and multi-hit models
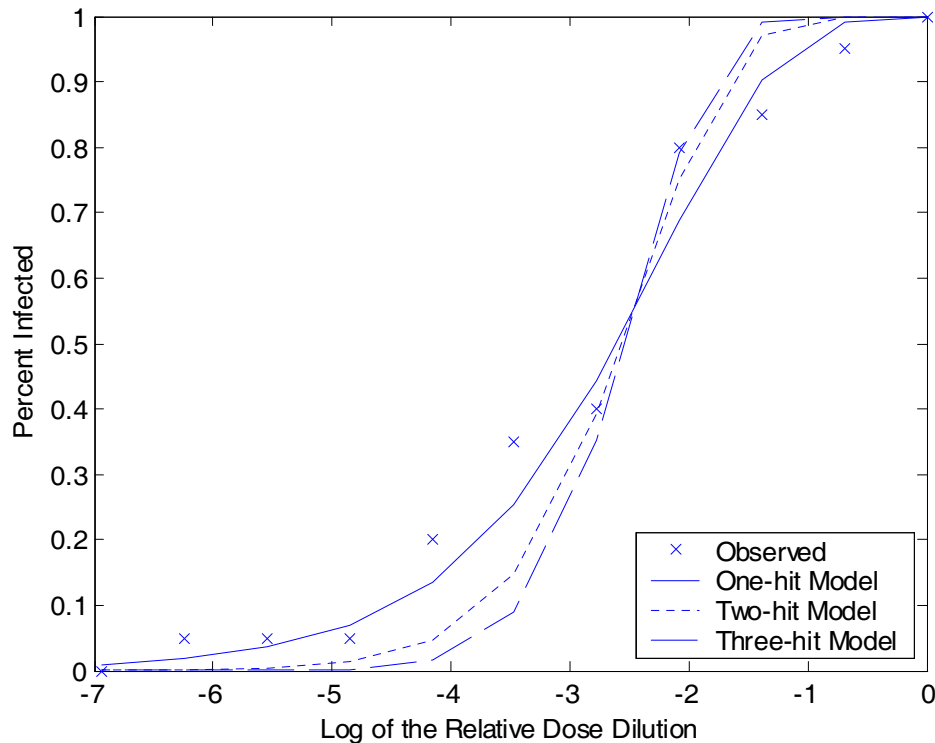
$$(4) \qquad p = 1 - \sum_{j=0}^{t-1} \frac{(\lambda\kappa)^j \exp(-\lambda\kappa)}{j!}$$

where t is the number of organisms required to initiate infection, in this case, t = 2 or 3. Written in a form analogous to Equation 3, the model is as follows:

$$(5) \qquad p_i = 1 - \sum_{j=0}^{t-1} \frac{(\alpha_i M)^j \exp(-\alpha_i M)}{j!}$$

The same method used to fit the one-hit model was applied to the two-hit and three-hit models. The maximum likelihood estimates of the parameter M, the Pearson's chi-square statistics, and p-values are presented in Table 2. The p-values < .001 for the two-hit and three-hit models indicate that these models fit the data poorly. Further, graphical depictions of the multi-hit models (Figure 1) indicate that they under-predict infection risk at low doses and over-predict infection risk at high doses relative to the observed proportions infected.

Similar methods were used to fit the one-hit model to the infection response data obtained by exposing groups of 24 to 29 guinea pigs to respirable aerosols containing *C. burnetii*; the aerosol particles were primarily 1 μm in diameter. The results of the maximum likelihood estimation are presented in Table 2, where $\hat{M}$ was determined to be 175.08. As Figure 2 illustrates, the one-hit model compares well to the observed infection data. The Pearson's chi-square statistic for the observed versus predicted responses was $\chi^2_3 = 0.0993$; note that the original dose groups 4 through 6 in Table 3 were combined to obtain an expected response in the aggregated group close to the suggested minimum of 5. The associated *p*-value was 0.992, which signifies that the observed response data do not differ significantly from the response data predicted by the one-hit model with M = 175.08. As with the injection experiments in guinea pigs, we fit two-hit and three-hit models and observed that the fit of the multi-hit mod-

Table 2
Estimated Parameters, Pearson's Chi Squared Statistics and p-Values of the *C. burnetii* One-hit and Multi-hit Infection Models

| Model	$\hat{M}$	χ^2	df	p-value
Guinea Pig Injection Data				
One-hit	9.346	1.757	6	0.941
Two-hit	21.636	32.123	6	<0.001
Three-hit	33.778	113.33	6	<0.001
Guinea Pig Aerosol Data				
One-hit	175.08	0.0993	3	0.992
Two-hit	377.976	9.9651	3	0.019
Three-hit	564.00	43.569	3	<0.001
Human Aerosol Data				
One-hit	951.57	10.198	2	0.006
Two-hit	703.23	120.895	2	<0.001
Three-hit	703.23	669.786	2	<0.001

Table 3
Experimental Data and Expected Response of Guinea Pigs Exposed to *C. burnetii* via Inhalation of Respirable Aerosols

Dose Group	Dilution (d_i)	α_i	Observed Response*	$\hat{p}_i$	$\hat{p}_i(\hat{M})$	Expected Response*
1	10^{-1}	1	24/24	1	1	24/24
2	10^{-2}	1/10	28/28	1	1	28/28
3	10^{-3}	1/100	22/27	0.8	0.83	22/27
4	10^{-4}	1/1000	4/24	0.2	0.16	3.8/24
5	10^{-5}	1/10,000	1/26	0.04	0.02	0.45/26
6	10^{-6}	1/100,000	0/29	0	0.01	0.05/29

*Infected/Exposed

Figure 2

Observed infection frequencies in guinea pigs exposed via the
respiratory route and infection frequencies expected from the model
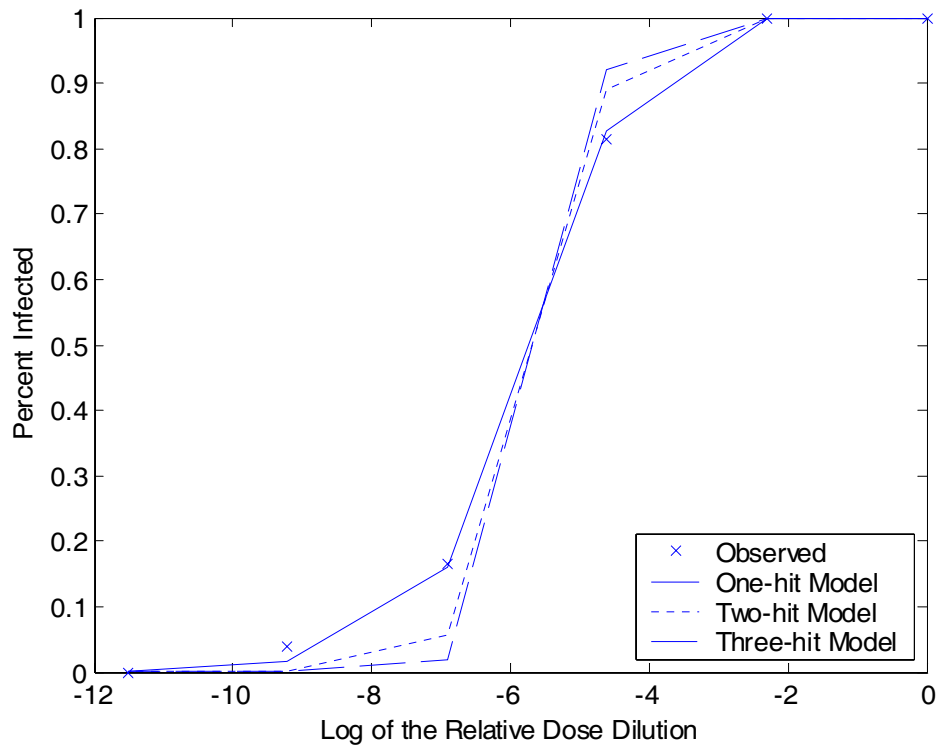
els were poor compared to the one-hit model, namely, the p-values for the multi-hit models are < 0.01 (Table 2). In addition, the predicted infection probabilities diverge progressively from the observed infection proportions when evaluated graphically, as seen in Figure 2.

These analyses provide strong evidence that a single *C. burnetii* organism is capable of infecting the guinea pig, and it is reasonable to speculate that infection by *C. burnetii* in humans also adheres to a one-hit model. In that regard, Tigertt, Benenson, and Gochenour (1961) reported on the response of humans exposed to *C. bur-*

netii through the inhalation of respirable aerosols, primarily 1 μm in diameter (Table 4). Using the same methods outlined above, the one-hit model was fit to the observed data with $\hat{M}$ determined to equal 951.57. However, the predicted risks of infection based on the one-hit model poorly fit the observed proportions infected, as seen in Figure 3. The Pearson's chi-square statistic for the observed versus predicted responses was $\chi_2^2 = 10.197$; note that the original Table 4 dose groups 1 and 2 were combined, and the original Table 4 dose groups 4 through 7 were also combined, to achieve an expected response in

Table 4

Experimental Data and Expected Response of Human Subjects Exposed to *C. burnetii* via Inhalation of Respirable Aerosols

Dose Group	Dilution (d_i)	α_i	Observed Response*	$\hat{p}_i$	$p_i(\hat{M})$	Expected Response*
1	10^{-1}	1	2/2	1	1	2/2
2	10^{-2}	1/10	4/4	1	1	4/4
3	10^{-3}	1/100	4/5	0.8	0.99	4.9/5
4	10^{-4}	1/1000	7/8	0.9	0.55	4.4/8
5	$10^{-4.5}$	1/3200	3/3	1	0.15	0.45/3
6	10^{-5}	1/10,000	4/5	0.8	0.01	0.39/5
7	10^{-6}	1/100,000	0/2	0	0.01	0.02/2

*Infected/Exposed

Figure 3
Observed infection frequencies in humans exposed via the
respiratory route and infection frequencies expected from the model
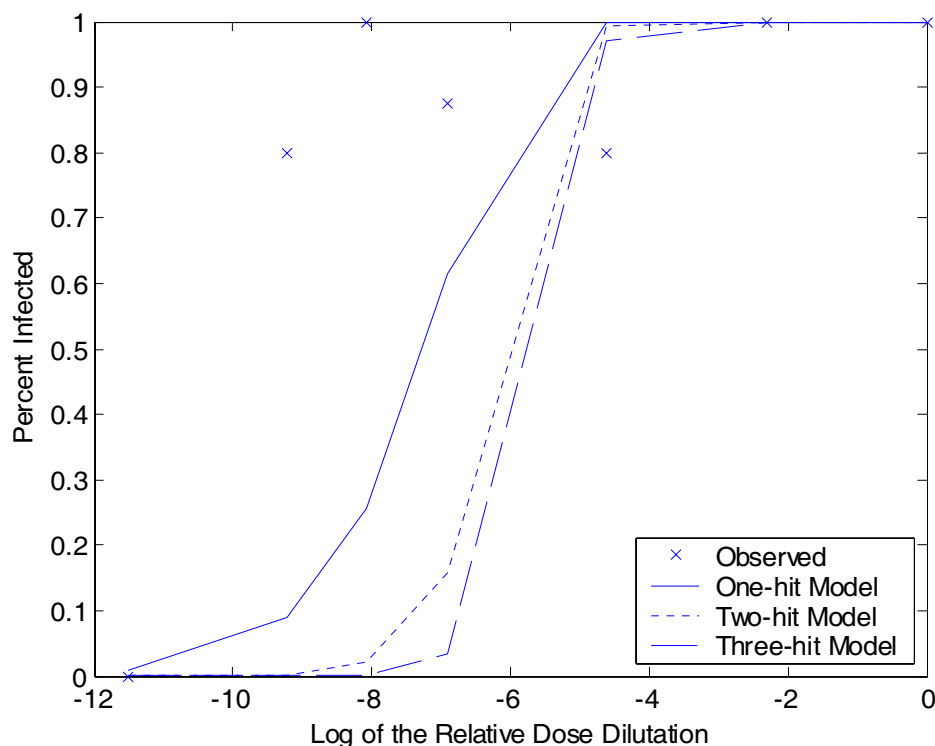
the aggregated groups close to the suggested minimum of 5. The associated *p*-value was 0.006, which nominally means that the observed response data differ significantly from the response data predicted by the one-hit model with M = 951.57. However, the small sample sizes in the human dose groups (2 to 8 subjects) clouds the interpretation of a goodness of fit test based on an asymptotic chi-square distribution. In addition, Tigertt, Benenson, and Gochenour (1961) did not report the concentration of viable *C. burnetii* in the undiluted egg slurry used in their human study, so the actual expected dose values are unknown. Uncertainty in the doses used, combined with large sampling variability due to small numbers of subjects, makes it impossible to meaningfully distinguish between alternative models (including the one-hit model) for the human inhalation dose-response function.

The guinea pig study by Tigertt and colleagues does permit estimating κ, the per organism probability of infection. Their report indicates that the probable concentration of infectious *C. burnetti* in the undiluted egg slurry, c_0, used in the guinea pig experiments was 20×10^9 mL^{-1}, as determined by titration on an unspecified medium. The concentration determined by direct counting, which would identify all organisms present regardless of infectious capability, was of the same order of magnitude. The latter finding suggests that κ is in the range

[0.1, 1]. A point estimate of κ was extrapolated from the fitted model based on the median infectious dose in guinea pigs exposed via intraperitoneal inoculation. Based on Equation 3 with M = 9.379, setting p = 0.5 requires that the product $\alpha \times 9.379$ equal 0.693, such that $\alpha = 0.0741$. The exact dilution factor d is obtained from the product $\alpha \times d_1$, and corresponds to 3.7×10^{-11} = $10^{-10.43}$. To obtain p = 0.5 based on Equation 2, it is also required that the product $c_0 \times d \times v \times \kappa$ equal 0.693. Given v = 1 mL, $c_0 = 20 \times 10^9$ mL^{-1}, and d = $10^{-10.43}$, it follows that $\kappa = 0.933$; that is, the probability that a single organism of *C. burnetii* will infect a guinea pig exposed via intraperitoneal injection is approximately 0.9.

It is possible that we are applying circular logic in estimating κ, because to determine the *C. burnetii* concentration in their undiluted egg slurry Tigertt and colleagues reportedly used an unspecified titration experiment following the principles outlined by Parker (1938). This approach is similar to the one outlined here in that it utilizes Poisson's law of small numbers to predict infection response in the circumstance of serial dilutions of the inoculum. Because the guinea pig data are well described by a one-hit model, Tigertt and colleagues may have extrapolated the concentration in the original slurry from the intraperitoneal injection by assuming that every organism could produce infection with probability one.

In that circumstance, the slight deviation from $\kappa = 1$ that we found would arise from discrepancies between our model fit and that of the original investigators. However, we cannot assess such discrepancies because Tigertt and colleagues did not describe their model, their estimated model parameters, or any assessment of their model's goodness of fit. This issue could be clarified by applying the same approach to the respiratory aerosol experiments with guinea pigs and humans. Unfortunately, that analysis is not possible because the investigators did not report the absolute aerosol concentrations to which the subjects were exposed.

Person-to-Person Airborne Transmission

Because it is clear that *C. burnetii* can infect humans via inhalation, the potential for person-to-person transmission via inhaling respiratory aerosol depends on the extent of emission of viable pathogens from infected persons. Secondary transmission is "rare" in general (Centers for Disease Control and Prevention, 2004), but reports of nosocomial transmission to patients and health care workers (Derrick, 1953; Deutsch & Peterson, 1950; Osorio et al., 2003) and of transmission via contaminated laundry (Oliphant et al., 1949) indicate that viable rickettsiae are released by Q fever patients; however, these reports do not establish that *C. burentii* was released in respiratory aerosol. At the same time, *C. burnetii* have been visualized by light microscopy in the expectorant of Q fever patients, and presence of the organism in sputum is used for early diagnosis of Q fever (Steinmann, 1951). The presence of *C. burnetii* in the sputum is consistent with the observation of large numbers of rickettsiae in the pulmonary alveoli postmortem (Whittick, 1950). The incidence of Q fever in the context of autopsy (Harman, 1949; Gerth, Leidig, & Riemenschneider, 1982) and parturition (Ludlam et al., 1997; Syrucek, Sobeslavsky, & Gurvirth, 1958) also indicates that viable *C. burentii* are present in other body tissues including placental blood and amniotic fluid, as has been observed in guinea pig tissues (Parker, 1943). Unfortunately, there are no published data on the concentration of *C. burnetii* in any body fluid. Overall, we believe the evidence supports the idea that person-to-person transmission of *C. burnetii* via the inhalation of respiratory aerosol is possible, although the low frequency of reported person-to-person transmission suggests that the pathogen's concentration in respiratory fluid is low.

Conclusions

We conclude the evidence overall suggests that a single *C. burnetii* organism can initiate infection in humans exposed through the respiratory tract. In addition, it ap-

pears that a single organism has a probability on the order of 0.9 to initiate infection in the guinea pig. There is no indication that humans are less susceptible than guinea pigs to infection by *C. burnetii*, and we note that the probability that a single organism initiates infection is higher than that generally seen with smallpox virus for which $\kappa \approx 0.1$ (Nicas, et al., 2004). An infectious dose of one organism with $\kappa \approx 0.9$ would explain the high infectivity of *C. burnetii* seen in environmental transmission of Q fever to humans. The one-hit model combined with our κ estimate would mean that previous World Health Organization (1970) estimates of casualties resulting from use of *C. burnetii* as a biological weapon, which presume an infectious dose of 10 organisms, are negatively biased.

We also conclude that the potential exists for person-to-person airborne transmission of Q fever. The organism is present in lungs (Whittick, 1950) and respiratory excretions (Steinmann, 1951) of at least some patients. Coughing is associated with some proportion of Q fever cases and emits many particles of respiratory fluid that quickly attain diameters less than 100 μm; these particles can be inspired and, depending on particle aerodynamic diameter, deposit in the alveolar region or upper respiratory tract. However, the estimated degree of risk depends on the pathogen's concentration in respiratory fluid, as well as the expiratory event rate, the size and volume distribution of particles emitted per respiratory event, the receptor's breathing rate and exposure duration, and the receptor's location in the room relative to the source case (Nicas, Nazaroff, & Hubbard, 2004). Given the high infectivity of *C. burnetii*, we hypothesize that the low frequency of person-to-person transmission of Q fever is due to low concentrations of the organism in respiratory fluids.

Knowledge of the infectious dose of *C. burnetii* (i.e., one organism with $\kappa \approx 0.9$) also permits estimating inhalation infection risk due to a laboratory procedure or accident if one knows the pathogen concentration in the materials being handled and can estimate the size and volume distribution of aerosolized particles, along with the aforementioned receptor parameters. A quantitative estimate of infection risk, even if uncertain, serves to inform biosafety officers in their decision making about infection control procedures.

Acknowledgements

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